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CASE REPORT

Pediatric papillary tumors of the pineal region: to observe or to treat following gross total resection?

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Abstract
Introduction Papillary tumors of the pineal region (PTPR) are rare brain tumors characterized by frequent local recurrences. Standardized treatment strategies are not yet defined.
Case report We present the case of a 3-year-old girl diagnosed with PTPR. Due to her young age, adjuvant radiotherapy was omitted after gross total tumor resection. Thirty-six months later, local tumor recurrence occurred. Considering the possible risks of secondary surgery, the recurrent tumor was irradiated with proton radiotherapy. Three months later, the tumor showed near-complete remission.
Discussion Based on this experience and other pediatric case reports from the literature, local radiotherapy might be suggested also after complete tumor resection.

Keywords Brain tumor · Child · Proton beam irradiation · Outcome

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Introduction

Tumors of the pineal region account for about 3–4 % of all brain tumors in childhood [4]. Papillary tumors of the pineal region (PTPR) represent a rare and histologically distinct subgroup of tumors originating in this area [3, 10]. First described by Jouvet et al. in 2003 [10], PTPR have been included in the 2007 World Health Organization Classification of Tumors of the Nervous System as a separate tumor entity [15]. Among 70 PTPR reported to date, examples are recognized in both children and adults with ages ranging from 5 to 67 years (mean, 34 years) [14]. PTPR has a distinctive epithelial character and shows both solid and papillary architecture [6, 10, 14]. Immunohistochemical analysis is crucial to distinguish PTPR from morphological similar pineal tumors, mainly papillary ependymoma and choroid plexus papilloma [8]. PTPR express strong immunoreactivity for CK18, S100, NCAM, neuron-specific enolase (NSE), and vimentin [5, 6]. Due to the specific localization of this entity in the region of the posterior commissure and the distinctive immunohistochemical profile, PTPR is presumed to arise from the specialized ependyma of the subcommisural organ [10]. Recent ultrastructural studies have demonstrated that PTPR has concomitant ependymal, neuroendocrine, and secretory features, lending further support

to this hypothesis [2]. Despite advances in immunohistochemistry and cytogenetics, the biological behavior of PTPR is still not fully understood. Thus, uniform therapeutic guidelines have not yet been established. Here, we describe a case of PTPR in a 3-year-old girl with 3.5 years of clinical and neuroradiological follow-up.

Case report

Clinical presentation

A 3-year-old girl presented to her pediatrician with a history of new-onset headaches accompanied by nausea, lasting for several hours a day. The neurological examination was normal and migraine was initially suspected. After symptoms persisted for 2 weeks, cranial magnetic resonance imaging (MRI) was performed. The MRI revealed a cerebral mass located in the pineal region measuring 2×2.8×3.5 cm (Fig. 1a). The tumor displayed dorsal cystic structures and a ventral solid portion with inhomogeneous contrast agent enhancement leading to a compression of the tectum. The consecutive aqueductal stenosis resulted in occlusive hydrocephalus. A ventriculostomy of the third ventricle was performed to reduce intracranial pressure. Tumor markers such as AFP and beta-HCG in serum and cerebrospinal fluid (CSF) were within the normal range. Two weeks later, the patient underwent gross total tumor resection through a suboccipital supracerebellar approach. Postoperative imaging demonstrated complete resection (Fig. 1b). On postoperative clinical examination, the girl was found to have a vertical supranuclear gaze palsy, convergence deficit, and mid-dilated pupils (Parinaud's syndrome). This functional deficit led to gait instability, particularly when climbing stairs.

Further treatment options were thoroughly discussed. Given the young age of the patient and macroscopically gross total tumor resection, the decision was made to omit adjuvant radiotherapy. The girl was followed at 3-month intervals by clinical examinations and cranial MRI. Control intervals were expanded to once every 6 months during the second postoperative year. The clinical course was uneventful, except for persistent vertical gaze palsy. Local tumor recurrence was detected on routine follow-up cranial MRI after 3 years (Fig. 1c). The solid and partially cystic recurrent tumor was located within the third ventricle dorsal inferior of the interthalamic adhesion without disturbance of the CSF circulation, approximately 1.8×0.7×1.3 cm in size. At this time, the patient did not show any additional neurological symptoms. The possibility of a second surgery was rejected considering the potential risks of additional neurological damage. Subsequently, it was decided to treat the recurrent tumor with proton beam irradiation, with a total dose of 54 Gy (RBE) in 30 fractions of 1.8 Gy (RBE) per fraction, five fractions a week. At first follow-up, 3 months after completion of therapy, the MRI demonstrated near-complete remission (Fig. 1d).

Histological diagnosis

Histopathological examination revealed a moderately cellular, epithelial tumor with solid and papillary growth patterns (Fig. 2). Perivascular pseudorosette formation was a prominent feature; however, true rosettes could not be demonstrated. The cytoplasm of the neoplastic cells varied from clear to amphophilic. Areas of necrosis were present and mitotic activity was moderate (4–6/10 HPF). Immunohistochemical analysis showed positive cytoplasmic staining for NSE and MAP2, while S100 protein was inhomogeneously expressed. Some tumor cells, mostly those forming papillary structures, displayed positivity for Pan-cytokeratin. Glial fibrillary acidic

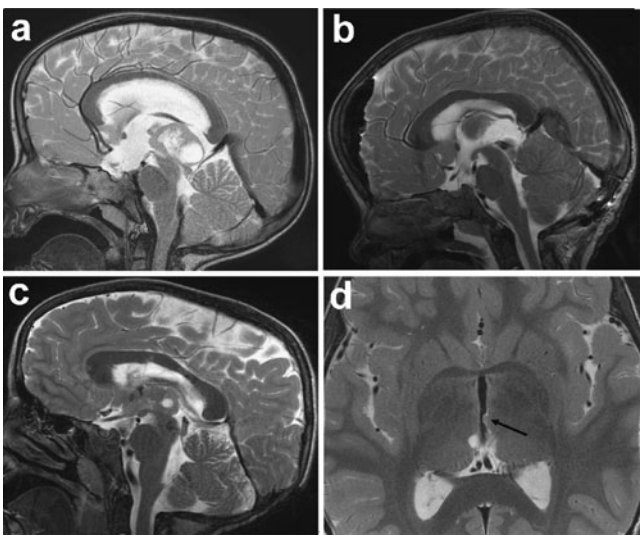

Fig. 1 **a** Sagittal preoperative T2-weighted MRI showing a cerebral mass with cystic portions located in the pineal region. **b** Sagittal postoperative T2-weighted MRI demonstrates complete resection. **c** Local tumor recurrence 36 months after complete resection. **d** Axial T2-weighted MRI obtained after proton beam therapy. A small residual tumor is seen only on axial slices (*arrow*)

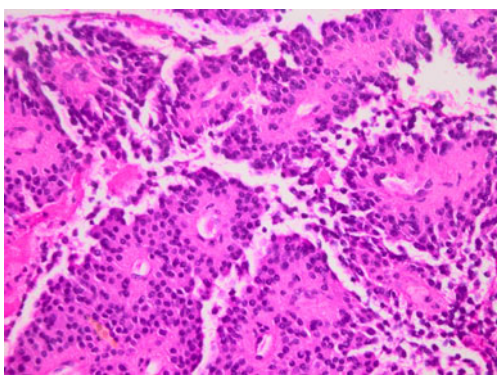

Fig. 2 Histopathological features of PTPR demonstrating solid and papillary growth pattern with perivascular pseudorosette formation

Table 1 Pediatric patients with PTPR. Treatment modalities and outcome

Case [reference]	Age (years)	Sex	Tumor size (mm)	Operation	Adjuvant therapy	Follow-up (months)	Recurrence (months)	Salvage therapy
1 [12]	1 3/12	M	10	IR	CT, RT	15	NA	NA
2 [6]	5	F	28	CR	CT	24	21	CR, RT
3 [6]	11	F	30	IR, CR	CT, RT	79	72	CR, CT, RT
4 [6]	13	M	NA	CR	RT	5	NA	NA
5 [1]	13	M	31	CR	RT	15	NA	NA
6 [6]	14	M	NA	CR	NA	NA	NA	NA
7 [6]	14	M	50	CR	CT	102	44, 53, 88	RT

NA not available, *M* male, *F* female, *CR* complete resection, *IR* incomplete resection, *CT* chemotherapy, *RT* radiotherapy

protein immunolabeling was minimal and restricted to perivascular areas, particularly adjacent to blood vessels. Staining for other neuronal markers like N-Neu, chromogranin A, neurofilament 200, neurofilament 70, and synaptophysin was negative. The Ki67 proliferation index was up to 10–15 %.

Discussion

Grading criteria and therapeutic protocols for PTPR have not yet been established because of the rarity and relatively new diagnosis in the 2007 World Health Organization Classification of Tumors of the Nervous System. Considering its frequent local recurrence, PTPR is thought to correspond at least to WHO grade II/III. To gain further insight into tumor characteristics, genetic analysis has been performed by comparative genomic hybridization and gene expression studies [7]. Losses on chromosome 10 and 22q and gains on chromosomes 4, 8, 9, and 12 have been detected. Gene expression analysis has shown upregulation of genes such as ZH4, RFX3, TTR mRNA, and CGRP [5, 8]. Clinical implication of these findings has not yet been elucidated.

Since its original description by Jouvet et al. in 2003, about 70 cases have been reported in literature [14, 16]. Among these patients, seven were children under 16 years of age (Table 1) [1, 6, 12]. Clinical manifestations include headache, diplopia, dizziness, and vomiting [1, 11, 12, 14]. Spinal dissemination is rare at the time of diagnosis. A key feature of PTPR is their high risk for local recurrence. Three out of six pediatric patients suffered from local tumor recurrence, the others were lost to follow-up [1, 6, 12]. Poulgrain et al. investigated the 5-year- and 10-year progression-free survival of all reported cases to date, which has been estimated at 34.5 and 8.6 %, respectively [14]. Fèvre-Montange et al. performed univariate analysis to test the prognostic significance of clinical variables such as age, gender, tumor size, gross total tumor resection, and adjuvant radiotherapy [6]. The only clinical factor that tended to be associated with overall survival and recurrence was the extent of resection [6].

Standardization of treatment regimen is not yet determined due to the lack of reliable clinical and biological predictors and the small number of cases with careful follow-up. Maximal surgical tumor resection is suggested as the first-line procedure. Radiotherapy and chemotherapy have been adopted as further treatment options [14]. Radiotherapy has been applied in about two thirds of all reported patients using different protocols and methods [14]. In the current report, radiotherapy was initially avoided because of the young age of the patient and total tumor resection. However, tumor relapse occurred 3 years after diagnosis, confirming the high risk of local recurrence in PTPR. With respect to the apparent high propensity of local recurrence, adjuvant radiotherapy might be applied in older children with gross total tumor resection. In younger children, the cerebral developmental vulnerability has to be taken into account. However, in case of recurrence, radiotherapy seems to be an effective therapy. Especially in young patients, proton beam irradiation needs to be considered in order to reduce the integral dose reduction to the adjacent normal tissue [9, 13, 17, 18].

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